WS6.1 Longitudinal associations between FEV1 and HbA1c in a UK cohort of young people with cystic fibrosis

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Objectives: To interrogate the UK national data set and explore longitudinal relationships between FEV1, HbA1c and OGTT parameters in young people with CF up to the age of 23 years.
Methods: The UK CF data set (2007 to 2012) recording annual measurements of height, weight, BMI, % predicted FEV1 & FVC, HbA1c and 2hr glucose (2hrGlu) (>10 yr only) was interrogated. HbA1c values >6.5% and 5.7–6.5% were used to define 'undiagnosed' DM and PD respectively, in patients not labelled as having CFRD. Data from cases with known CFRD and DM were censored. Longitudinal models analysed %FEV1 and %FVC as dependent variables, and HbA1c or 2hrGlu, BMI SDS, and age as covariates in patients with HbA1c in the PD range.
Results: 2105 patients (1097 males, 87.9% with DF508 mutations, median (range) age 13.7 (5.6–22) y, mean±SD BMI Zscore –0.11±1.1, %FEV 82.1±20.3 at first visit were included. Median (range) follow up was 3 (1–5) years. 2hrGlu was available in a subgroup (n = 636). Changes in HbA1c (Table 1), but not 2hrGlu (slope –0.1, p = 0.3), within the PD range (5.7–6.5%) were inversely associated with %FEV1.

Table 1. Univariate longitudinal models incorporated

Dependent variable	Slope (per % higher HbA1c)	P value	95% Confidence interval
%FEV1	–2.9	0.016	–5.1 to –0.5
%FVC	–2.1	0.08	–4.4 to 0.3

Conclusion: In this large UK data set, longitudinal increases in HbA1c within the PD range were associated with declining lung function. Our findings support the rationale for trials to intervene early to manage hyperglycaemia in young CF patients with PD.
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WS6.2 Glucose tolerance in pediatric patients with cystic fibrosis

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Background: Cystic fibrosis (CF)-related diabetes (CFRD) is a leading complication of CF and is associated with pulmonary and nutritional deterioration. Pathogenetic mechanism include insulin deficiency and insulin resistance.
Objectives: To evaluate glucose tolerance in pediatrics patients with CF and to define a possible role of puberty in changing the status of glucose tolerance.
Methods: Data of CF patients who performed an oral glucose tolerance test (OGTT) in the period 2003–2013 were collected. Glucose, insulin and C-peptide concentrations were determined every 30 minutes for 3 hours. The area under the glucose and insulin curve (AUC), the index of insulin resistance (HOMA-IR) and the insulinogenic index (IG) were also calculated.
Results: We analyzed OGTT of 173 CF patients [91 females; median age (IQR) 13.2 yrs (2.4); 91 pre-pubertal (8–12 yrs) and 82 pubertal (13–17 yrs)]. 12% of patients had glucose intolerance, 5% had diabetes without fasting hyperglycemia, 1% had diabetes with fasting hyperglycemia and 6% had indeterminate glucose tolerance. There was no significant differences in HOMA-IR, IG, FEV1%pred. and BMI percentile among different tolerance categories. In contrast pubertal patients had higher HOMA-IR and IG than pre-pubertal (P = 0.001 and P = 0.006, respectively) and a trend towards higher AUC $_{(ins0–120)}$.
Conclusion: The data suggest that glucose tolerance status in our CF pediatric population is not related to pulmonary function and nutritional status. The degree of insulin resistance seems to increase around pre-puberty.

WS6.3 Subtle defects in glucose metabolism prior to development of diabetes in patients with cystic fibrosis

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Cystic fibrosis related diabetes (CFRD) is a common co-morbidity in people with CF. The underlying pathophysiology of CFRD has not been revealed. We hypothesized that it might be associated with an abnormal gut derived hormonal profile, specifically of lower incretin hormone responses, prior to development of CFRD.
Ten non-diabetic CF patients (5F/5M) and nine healthy controls underwent an oral glucose tolerance test (OGTT) for evaluation of insulin secretion, sensitivity and incretin dynamics.
Fasting and 2-hour glucose levels of patients with CF were significantly higher compared to healthy controls. In the patients with CF the peak glucose occurred later (60 min vs. 30 min in controls) and was higher (205.5±12.8 mg/dL vs. 117.2±9.88 mg/dL compared to normal controls. Insulin levels were significantly lower in the CF group at 30-min, compared to control group. C-peptide levels were significantly lower in the CF group at fasting and all time points and they had a lower and delayed peak compared to controls. AUC for GLP-1and GIP was significantly lower for CF patients compared to control (p = 0.02, p = 0.04 respectively). CF patients had lower insulin sensitivity (p = 0.022), a lower acute insulin response (p < 0.0001) and the oral disposition index was significantly lower in CF patients compared to controls (p < 0.0001) as well as the insulin clearance (p = 0.002).
We propose that impaired incretin hormone responses is an additional contributor to the pathophysiology of CFRD. This may be due to lower secretion responses or due to reduced effects at the cellular level.

WS6.4 A placebo-controlled trial of insulin therapy with or without adjuvant metformin in patients with cystic fibrosis-related diabetes (CFRD)

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Objectives: Diabetes is a major co-morbidity in patients with Cystic Fibrosis (CF) with a prevalence of 31% in our adult CF population and is associated with clinical deterioration. CFRD consists of both insulin deficiency and fluctuating insulin resistance. We hypothesized that adding metformin to insulin therapy results in a better management of CFRD. Aim of this study was to investigate the effect of adjuvant metformin therapy on insulin need and glycaemic control in CFRD.
Methods: In this prospective randomized triple-blind crossover placebo-controlled study, 17 patients received insulin therapy and were randomized for either receiving adjuvant metformin or placebo during the first 3-month therapy period. After a four week wash-out, patients were interchanged to the other therapy regimen for a second 3-month therapy period. Study parameters were insulin need and blood HbA1c and glucose levels.
Results: 14 patients completed the study. The median number of units insulin administered per day was significantly lower during the metformin study period in comparison to the placebo period (respectively 19 IE/day and 26 IE/day, p = 0.015). The lowering was more outspoken in patients with high insulin needs. HbA1c remained unchanged between both treatment periods (51.5 versus 55 mmol/mol, p = 0.237). Glucose profiles measured by continuous glucose monitoring were more stable during the metformin treatment.
Conclusion: In patients with CFRD, insulin need lowered and glucose levels were more stable after adding metformin to their standard therapy.